

Serum lipocalin-2 levels are increased in patients with psoriasis

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Summary

The protein lipocalin (LCN)-2 is known to be related to insulin resistance, obesity and atherosclerotic diseases. Psoriasis is an inflammatory skin disease related to metabolic syndrome. The aim of this study was to examine the relationship between serum LCN2 levels and indicators for metabolic syndrome and inflammatory cytokine levels in patients with psoriasis. Serum LCN2 levels were measured in patients with psoriasis, atopic dermatitis (AD) or bullous pemphigoid (BP), and compared with those of healthy controls. Serum LCN2 levels were also compared with several indicators for metabolic syndrome, and with serum levels of interleukin (IL)-6 and tumour necrosis factor (TNF)- α , two markers of inflammation. Serum LCN2 levels in patients with psoriasis were significantly higher than those of healthy controls, but there was no significant correlation between serum LCN2 and body mass index. Serum LCN2 levels also correlated with serum IL-6 and TNF- α levels in patients with psoriasis. Serum LCN2 levels are a general indicator for increased inflammation in the patients with psoriasis.

Lipocalin (LCN)-2, also known as neutrophil gelatinase-associated lipocalin, is a member of the lipocalin family of proteins, which share a barrel-shaped tertiary structure with a hydrophobic pocket that can bind lipophilic molecules. LCN2 is expressed in various tissues or cells, including liver, lung, kidney, adipocytes, macrophages and epithelial cells.^{1,2} LCN2 functions as an antimicrobial protein.^{3,4} In addition, LCN2 is known to be related to insulin resistance, obesity and atherosclerotic diseases.⁵ Patients with psoriasis have a higher prevalence of obesity, hypertension, diabetes and cardiovascular diseases than healthy controls.⁶ Thus, to study the relationship between LCN2 and psoriasis, we examined serum LCN2 levels in patients with psoriasis and compared them with those of healthy controls, patients with atopic dermatitis (AD) and patients with bullous pemphigoid (BP). As for patients with psoriasis and healthy controls, we also studied the relationships

between serum LCN2 levels and several indicators for metabolic syndromes.

Report

The study was conducted with the approval of the institutional review board of University of Tokyo Hospital. All study participants provided written informed consent before participation.

Serum samples were obtained from 37 patients with psoriasis (10 women, 27 men; mean $\pm$ SD age 56.1 ± 14.0 years, range 25–78), 11 patients with AD (6 women, 5 men; age 31.4 ± 15.1 years, range 13–68), 12 patients with BP (8 women, 4 men; age 64.7 ± 18.9 , range 29–86) and 17 healthy controls (5 women, 12 men; age 38.6 ± 10.9 years, range 26–66). In the psoriasis group, 16 patients were using only topical treatment, while 11 were being treated with ciclosporin, 6 with oral etretinate and 4 with narrow-band ultraviolet (UV)B.

For the patients with psoriasis and the healthy controls, we calculated their body mass index (BMI), and also measured serum cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, interleukin (IL)-6, tumour

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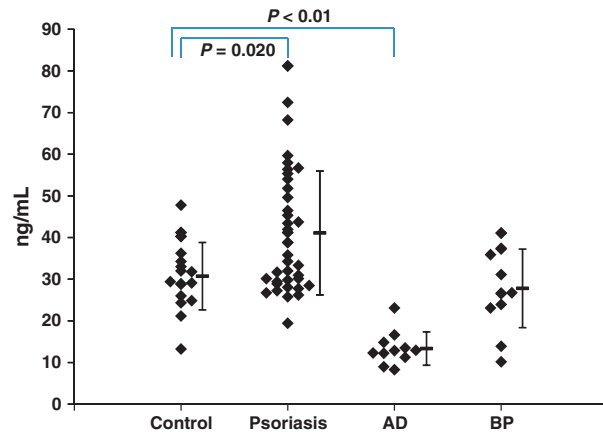


Figure 1 Serum lipocalin (LCN)2 levels in healthy controls and patients with psoriasis, atopic dermatitis (AD) or bullous pemphigoid (BP). Data are presented as mean $\pm$ SD.

necrosis factor (TNF)- α , plasma glucose and haemoglobin A1c during the fasting state in patients with psoriasis. The disease severity of psoriasis was assessed by the Psoriasis Area and Severity Index (PASI) (mean value 8.77 ± 2.40). Serum LCN2, IL-6 and TNF- α levels were determined by sandwich ELISA (R & D Systems, Minneapolis, MN, USA).

Statistical analysis was performed using the Wilcoxon rank sum test for comparison between two groups, and the Spearman rank-correlation analysis to examine the relationship between two continuous variables. $P < 0.05$ was considered significant.

We found that serum LCN2 levels were significantly higher in patients with psoriasis than in healthy controls (41.1 ± 14.9 vs. 30.7 ± 8.1 ng/mL; $P < 0.05$) (Fig. 1). For 17 patients with psoriasis (in addition to the enrolled patients) we also compared serum LCN2 levels before and after the following treatments: anti-TNF- α drugs ($n = 11$), narrowband UVB ($n = 5$) and oral ciclosporin ($n = 1$). Serum LCN2 levels were almost the same before and after these treatments (data not shown), even though almost all the patients responded well to their particular treatment. In contrast to patients with psoriasis, patients with AD had significantly lower serum LCN2 levels than did healthy controls (13.3 ± 4.00 vs. 30.7 ± 8.10 ng/mL; $P < 0.01$). There was no significant difference in serum LCN2 levels between patients with BP and healthy controls. As for the correlation between serum LCN2 levels and indicators for metabolic syndrome in patients with psoriasis and healthy controls, there was no significant correlation between serum LCN2 and BMI. Although serum LCN2 levels did not correlate with

PASI, serum triglyceride levels, serum total cholesterol levels, serum HDL cholesterol levels or plasma haemoglobin A1c levels, there was an inverse correlation of serum LCN2 with serum LDL cholesterol ($r = -0.52$, $P < 0.01$) and plasma glucose levels ($r = -0.66$, $P < 0.05$) in patients with psoriasis (Fig. 2). In contrast to the healthy controls (Fig. 3a), patients with psoriasis were found to have significant correlations both between serum LCN2 and IL-6 levels, and between serum LCN2 and TNF- α levels (Fig. 3b).

In this study, we found that serum LCN2 levels were significantly higher in patients with psoriasis than in healthy controls, whereas levels in patients with AD were significantly lower than in healthy controls. Guttman-Yassky *et al.*⁷ showed that expression of the LCN2 protein was increased in the epidermis of psoriatic skin lesions compared with AD lesions or normal skin. Interleukin (IL)-17 secreted from Th17 cells in the psoriatic skin lesions may induce LCN2 expression in the epidermis, as IL-17 *in vitro* induces LCN2 gene expression in keratinocytes. PASI did not correlate with serum LCN2 levels in our study, indicating that extracutaneous tissues might be the source of serum LCN2 protein in patients with psoriasis, although there is a possibility that this result could be due to our small sample size or the effect of treatment. Recently, Shen *et al.*⁸ identified LCN2 as a novel IL-17 target gene, and interestingly, reported that LCN2 gene expression is induced by IL-17 at the promoter level, either alone or in concert with tumour necrosis factor (TNF)- α . In accordance with their data, we found a significant correlation between serum LCN2 and TNF- α in patients with psoriasis. Because IL-17 and TNF- α are both pivotal cytokines in the pathogenesis of psoriasis, and their expression is not restricted to the skin, it is possible that extracutaneous tissues or cells, including peripheral blood cells, are also the source of serum LCN2 proteins in patients with psoriasis. In addition, serum LCN2 levels were lower in patients with AD, indicating the possibility that the AD microenvironment might suppress LCN2 production.

In our study, serum LCN2 level did not correlate with PASI. Furthermore, serum LCN2 level did not decline to baseline after successful treatment. As LCN2 is expressed in various tissues or cells, it is possible that LCN2 may not accurately reflect the degree of skin inflammation of patients with psoriasis, especially when tissue other than epidermis or dermis is also the major source for IL-6 and TNF- α . In fact, serum LCN2 seems to be a general indicator for systemic inflammation in psoriasis.

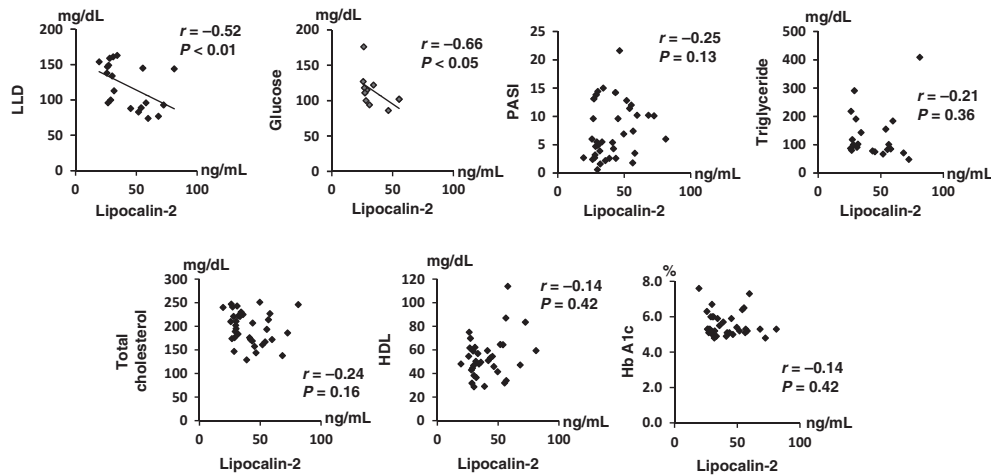


Figure 2 Correlation between serum lipocalin (LCN)2 level and serum low-density-lipoprotein (LDL) cholesterol, plasma glucose level, Psoriasis Area and Severity Index (PASI), serum levels of triglyceride, cholesterol and high-density-lipoprotein (HDL) cholesterol, and plasma levels of haemoglobin A1c in patients with psoriasis.

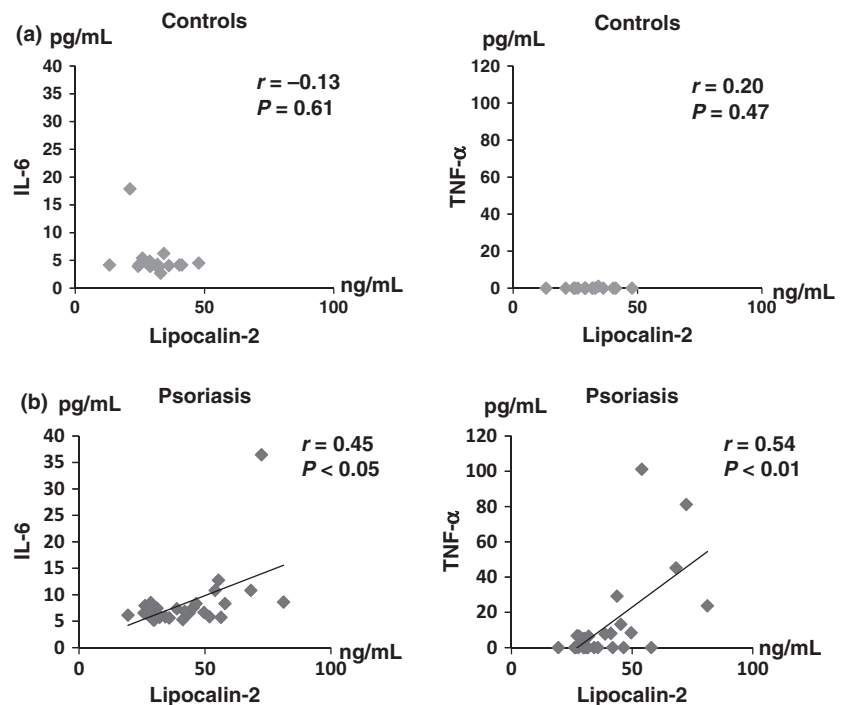


Figure 3 Correlation between serum lipocalin (LCN)2 level and serum interleukin (IL)-6 and tumour necrosis factor (TNF)-α levels in (a) healthy controls and (b) patients with psoriasis.

Although LCN2 is known as an adipocyte-secreted, metabolic syndrome-related protein, we did not find any significant correlation between LCN2 and BMI, either in patients with psoriasis or in healthy controls. Consistent with this, Stejskal *et al.*⁹ also reported no correlation between serum LCN2 levels and BMI in patients with metabolic syndrome. Furthermore, we found that serum

LCN2 levels were inversely correlated with serum LDL cholesterol and plasma glucose levels in patients with psoriasis, indicating that serum LCN2 levels are up-regulated in those patients with psoriasis with a lower risk of obesity-related diseases. We also found that serum LCN2 level correlated with serum IL-6 and TNF-α levels in psoriasis.

Conclusion

In this study, serum LCN2 levels were increased in patients with psoriasis without showing a positive correlation with indicators for metabolic syndromes, suggesting that LCN2 is a general indicator for increased inflammatory cytokines such as IL-6 and TNF- α especially in psoriasis, which has a Th17 background.

Learning points

- LCN2 is known to be related to insulin resistance, obesity and atherosclerotic diseases.
- Psoriasis is an inflammatory skin disease related to metabolic syndrome.
- Serum LCN2 levels in patients with psoriasis were significantly higher than those in healthy controls.
- There was no significant correlation between serum LCN2 and BMI.
- Serum LCN2 levels correlated with serum IL-6 and TNF- α levels in patients with psoriasis.
- Serum LCN2 levels are a general indicator for increased inflammation in patients with psoriasis.

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